Review of Peer-Reviewed Literature Regarding Dissolvable Tobacco Products

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Overview

- Purpose
- Approach
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Purpose

- Inform recommendations of the Tobacco Product Scientific Advisory Committee (TPSAC) by presenting a summary of the peer-reviewed literature on dissolvable tobacco products.

- ***Disclaimer****: Although the work reported was done under contract with FDA's Center for Tobacco Products, the content and conclusions of this presentation are those of RTI International.*

Approach

- As of 12/16/11, 25 peer-reviewed articles regarding dissolvable tobacco products were identified by FDA using the following:
  - PubMed
  - Science Citation Index
  - Social Sciences Citation Index
  - Google Scholar
  - PsychInfo
  - Business Source Corporate
- Search terms included dissolvable tobacco, novel, strip, stick, pellet, orb, toothpick, and brand names of products by manufacturers thought to market dissolvable tobacco products.

Approach

- Articles were submitted to RTI and reviewed by research epidemiologists Dr. Linda M. Brown and Stacy M. Endres.
- Of the 25 articles identified, 21 will be reviewed today. Information will not be presented on the four articles related to use of dissolvable tobacco products solely as cessation aids (e.g., as a drug) or potential modified risk tobacco products, two areas that TPSAC is not being asked to address.[1]
- Articles will be presented in chronological order; emphasis will be on dissolvable tobacco products. With the exception of one article published in 1991, all reviewed articles were published during 2006–2011.

[1]7/21/11, Presentation by Dr. David Ashley to TPSAC

Findings

Publication Year 1991—1 article

Nicotine Absorption and the Subjective and Physiologic Effects of Nicotine Toothpicks

Hasenfratz M, Bättig K. Clin Pharmacol Ther 1991;50:456–61.

Type of Study	Type of Dissolvable(s)	Sample Size (N) / Subject Description	Objective(s)	Authors Conclusion(s)
Randomized crossover study	▪ Nicotine-containing toothpicks (4 mg)	▪ N=12 ▪ Healthy female overnight abstinent smokers aged 20–39	▪ Assess amount of nicotine that can be absorbed from the toothpick, and investigate resulting physiologic and subjective effects compared to nicotine chewing gum (4 mg).	▪ Nicotine-laden toothpicks provide nicotine at rate equal to or faster than commercially available nicotine gums. ▪ Potential advantages of toothpicks: (1) dental care and (2) substitute for manipulative component of smoking act, remain to be verified in further experiments.

Funding Source: ESRO AG, Thalwil, Switzerland

Findings

Publication Year 2006—2 articles

New Tobacco Products: Do Smokers Like Them?

Caraballo RS, Pederson LL, Gupta N. Tob Control 2006;15:39–44.

Type of Study	Type of Dissolvable(s)	Sample Size (N) / Subject Description	Objective(s)	Authors Conclusion(s)
Focus group	▪ Ariva	▪N=140 ▪16 focus group sessions conducted with White, African American, and Hispanic male and female current smokers aged 30–50 ▪8 focus groups in Chattanooga, TN ▪8 focus groups in Dallas, TX ▪Both cities were test markets for Eclipse	▪ Understand how smokers learned about potentially reduced exposure products (PREPs) ▪Reason for first trying ▪Which ones they tried ▪First impressions ▪Reasons for continuing/ discontinuing use	▪Ariva tried by 12%, Eclipse by 90%. ▪Most did not like the PREPs and will not recommend them. ▪Most who used PREPs did so occasionally while continuing to smoke. ▪Health risks for combined use unknown.

Funding Source: Not specified

Tobacco-Specific Nitrosamines in New Tobacco Products

Stepanov I, Jensen J, Hatsukami D, Hecht SS. Nicotine Tob Res 2006;8:309–13.

Type of Study	Type of Dissolvable(s)	Sample Size (N) / Subject Description	Objective(s)	Authors Conclusion(s)
Basic science study	▪ Ariva tobacco lozenges ▪ Stonewall tobacco lozenges	▪ N=19 brands, including 6 new tobacco products (Ariva, Stonewall, Exalt, Revel, Smokey Mountain, and Quest), nicotine replacement products, conventional smokeless tobacco (SLT), and conventional cigarettes	▪ Compare tobacco-specific nitrosamine (TSNA) levels in new types of tobacco products with those in nicotine replacement products, conventional SLT products, and cigarette tobacco.	▪ Lowest TSNA levels in Ariva and Stonewall; highest levels in Exalt. ▪ Exalt levels comparable with levels in conventional commercial smokeless tobacco brands.

Funding Source: NIH grants CA81301 and DA13333

Findings

Publication Year 2007—3 articles

Changing Smokeless Tobacco Products New Tobacco-Delivery Systems

Hatsukami DK, Ebbert JO, Feuer RM, Stepanov I, Hecht SS. Am J Prev Med 2007;33:S368–78.

Type of Study	Type of Dissolvable(s)	Sample Size (N) / Subject Description	Objective(s)	Authors Conclusion(s
Review article	▪ Ariva tobacco lozenges ▪ Stonewall tobacco lozenges	Not applicable	▪ Describe the extant literature on newer SLT products directed at smokers, the current literature on the toxicity of these products, including nicotine addiction, and future directions for research.	▪ TSNAs highest in conventional and popular oral tobacco products; lowest in Ariva and Stonewall. ▪ NNAL concentrations similar for Ariva and medicinal nicotine (Commit). ▪ No data available on health effects of newer SLT low-nitrosamine products.

Funding Source: Transdisciplinary Tobacco Use Research Center (University of Minnesota) P50 DA013333

Nicotine Pharmacokinetics and Subjective Effects of Three Potential Reduced Exposure Products, Moist Snuff and Nicotine Lozenge

Kotlyar M, Mendoza-Baumgart MI, Li Z-Z, et al. Tob Control 2007;16:138–42.

Type of Study	Type of Dissolvable(s)	Sample Size (N) / Subject Description	Objective(s)	Authors Conclusion(s)
Randomized crossover study	▪ Ariva tobacco lozenges ▪ Stonewall tobacco lozenges	▪ N=10 males, aged 20–49 from the University of Minnesota and surrounding communities who had used Copenhagen SLT daily for at least 1 year	▪ Compare the pharmacokinetics and subjective responses of 3 new smokeless tobacco PREPs (Ariva, Revel, and Stonewall) to moist snuff and medicinal nicotine lozenge.	▪ Ariva and Stonewall result in lower nicotine concentrations and equivalent or lower reductions in subjective measures compared with medicinal nicotine. ▪ Potential of Ariva and Stonewall to cause diseases associated with smoking or SLT use largely unknown.

Funding Source: Transdisciplinary Tobacco Use Research Center P50 DA013333 and General Clinical Research Center Program grants K23 DA017307 and M01 RR00400 (University of Minnesota)

What Do Adult Smokers Think About Ads and Promotional Materials for PREPs?

O'Hegarty M, Richter P, Pederson LL. Am J Health Behav 2007;31:526–34.

Type of Study	Type of Dissolvable(s)	Sample Size (N) / Subject Description	Objective(s)	Authors Conclusion(s)
Focus group	▪ Ariva	▪ N=140 ▪ 16 focus group sessions conducted with White, African American, and Hispanic male and female current smokers aged 30–50 ▪ 8 focus groups in Chattanooga, TN ▪ 8 focus groups in Dallas, TX ▪ Both cities were test markets for Eclipse	▪ Describe adult smokers' reactions to PREP print advertisements and promotional materials for Omni, Accord, Advance Lights, Ariva, and Eclipse.	▪ 90% tried Eclipse; 12% tried Ariva. ▪ Ariva viewed as alternative when participants could not smoke. ▪ Many initially thought Ariva promotional material was for non-tobacco product. ▪ Men and women strongly offended by health warning about gum disease and tooth loss. ▪ Important for public health community to monitor smokers' perceptions about novel tobacco products.

Funding Source: None

Findings

Publication Year 2008—3 articles

Nicotine Delivery, Cardiovascular Profile, and Subjective Effects of an Oral Tobacco Product for Smokers

Blank MD, Sams C, Weaver MF, Eissenberg T. Nicotine Tob Res 2008;10:417–21.

Type of Study	Type of Dissolvable(s)	Sample Size (N) / Subject Description	Objective(s)	Authors Conclusion(s)
Clinical laboratory study	▪ Ariva tablets	▪ N=10 (5 men and 5 women) overnight abstinent cigarette smokers aged 18–50	▪ Examine the nicotine delivery, cardiovascular profile, and subjective effects of Ariva in cigarette smokers.	▪ Ariva delivered active doses of nicotine when 2–3 tablets were used simultaneously. ▪ Ariva suppressed several symptoms of tobacco abstinence/ withdrawal to varying degrees. ▪ Ariva's nausea-inducing and other adverse effects may limit acceptability.

Funding Source: U.S. Public Health Service grants R01 CA103827 and F31 DA018447

Potential Reduced Exposure Products (PREPs) for Smokeless Tobacco Users: Clinical Evaluation Methodology

Gray JN, Breland AB, Weaver M, Eissenberg T. Nicotine Tob Res 2008;10:1441–8.

Type of Study	Type of Dissolvable(s)	Sample Size (N) / Subject Description	Objective(s)	Authors Conclusion(s)
Clinical laboratory study	▪ Stonewall tobacco tablets	▪ Study 1: N=13 (12 men) White SLT users aged 18–50 who used ≤5 smoked tobacco products in past 6 months ▪ Study 2: N=19 (1 non-White) male SLT users aged 18–50 who used ≤5 smoked tobacco products in past 6 months	▪ Adapt efficient and reliable methods to examine withdrawal suppression and toxicant exposure associated with cigarette-like PREPs to examine short- and longer-term effects of PREPs for SLT users.	▪ Neither Stonewall nor placebo increased plasma nicotine. ▪ Compared with own brand, Stonewall had lower levels of cotinine and NNAL. ▪ Abstinence symptoms did not differ by tobacco source. ▪ Standardized evaluation strategies overseen by regulatory body needed for Stonewall and other PREPs prior to consumer release.

Funding Source: U.S. Public Health Service grant CA103827

Surveillance of Tobacco Industry Retail Marketing Activities of Reduced Harm Products

Slater S, Giovino G, Chaloupka F. Nicotine 2008;Tob Res 10:187–93.

Type of Study	Type of Dissolvable(s)	Sample Size (N) / Subject Description	Objective(s)	Authors Conclusion(s)
National survey	▪ Ariva	▪ N=4,126 tobacco retail stores ▪ Sites were based on sampling frame from the Monitoring the Future Study. ▪ Up to 30 retail outlets at each site were randomly selected for 10-minute field visit.	▪ Examine and understand availability and marketing of PREPs (including Ariva and Omni) in selected retail stores and price of PREPs vs. premium brand cigarettes.	▪ Ariva carried by 2.5% of stores. ▪ Ariva mean price lowest . ▪ Only 1 promotional offer for Ariva. ▪ Ariva most available in gas/ convenience stores and drug stores, suburban areas, and the South; least available in Hispanic neighborhoods. ▪ Ariva and Omni have long way to go to become viable and competitive alternatives to or substitutes for cigarettes.

Funding Source: Grant from Robert Wood Johnson Foundation to University of Illinois at Chicago for ImpacTeen project

Findings

Publication Year 2009—1 article

Consumer Awareness and Attitudes Related to New Potential Reduced-Exposure Tobacco Product Brands

Parascandola M, Auguston E, O'Connell ME, Marcus S. Nicotine Tob Res 2009;11:866–95.

Type of Study	Type of Dissolvable(s)	Sample Size (N) / Subject Description	Objective(s)	Authors Conclusion(s)
National survey	▪ Ariva ▪ Stonewall	▪ N=6,369 adult respondents in 2003; 5,586 in 2005 ▪ 19% current and 28% former smokers ▪ Data from White, Black, Hispanic, other, and non-Hispanic men and women ≥18 years obtained from NCI's Health Information National Trends Survey (HINTS 2003 and HINTS 2005).	▪ Provide national estimates of awareness and use of PREPs by brand and consumer interest in using PREPs.	▪ 45% heard of PREPs; 4.8% had tried. Awareness was 5.4% for Ariva, <1% for Stonewall. Awareness and use highest for current smokers. ▪ Interest higher in females and Whites, among daily/heavy smokers, and non-quitters. These smokers more likely to rate lung cancer risk as high and worry about developing lung cancer. ▪ Concern is that "health conscious" smokers may be especially vulnerable to PREP marketing messages.

Funding Source: None

Findings

Publication Year 2010—6 articles

Evaluating Oral Noncombustible Potential-Reduced Exposure Products for Smokers

Blank MD, Eissenberg T. Nicotine Tob Res 2010;12:336–43.

Type of Study	Type of Dissolvable(s)	Sample Size (N) / Subject Description	Objective(s)	Authors Conclusion(s)
Clinical laboratory study	▪ Ariva tobacco tablets	▪ N=21 White and non-White men and women smokers aged 18–55	▪ Measure the toxicant exposure and abstinence symptoms of suppression associated with the use of orally administered noncombustible PREPs for smokers using positive (OWN) and negative (No-T) control conditions.	▪ Ariva had lower acceptability ratings, CO and cotinine levels, and higher abstinence symptom ratings relative to OWN and higher NNAL levels relative to No-T. ▪ PREPs reduce exposure to CO, but ineffective abstinence symptom suppression and low acceptability may limit their viability.

Funding Source: NIDA grant PHS CA103827

A Pilot Randomized Study of Smokeless Tobacco Use Among Smokers Not Interested in Quitting: Changes in Smoking Behavior and Readiness To Quit

Carpenter MJ, Gray KM. Nicotine Tob Res 2010;12:136–143.

Type of Study	Type of Dissolvable(s)	Sample Size (N) / Subject Description	Objective(s)	Authors Conclusion(s)
Randomized trial	▪ Ariva tobacco lozenges ▪ Stonewall tobacco lozenges	▪ N=31 (19 male, 6 non-White) cigarette smokers, aged 18–65, not interested in quitting	▪ Test SLT use among smokers unmotivated to quit and its influence on smoking behavior and cessation.	▪ Ariva and Stonewall use led to 40% reduction in cigarettes/day with increases in measures of self-efficacy and readiness to quit smoking, but no increases in total tobacco use. ▪ Ariva and Stonewall could serve as a catalyst to increase motivation among smokers not wanting to quit. ▪ A large prospective randomized clinical trial to assess long-term use was suggested.

Funding Source: NIDA grants K23 DA020482 and K12 DA000357

Evaluating the Acute Effects of Oral, Non-Combustible Potential Reduced Exposure Products Marketed to Smokers

Cobb CO, Weaver MF, Eissenberg T. Tob Control 2010;19:367–73.

Type of Study	Type of Dissolvable(s)	Sample Size (N) / Subject Description	Objective(s)	Authors Conclusion(s)
Clinical laboratory study	▪ Ariva tobacco tablets	▪ N=28 (17 men, 14 non-White) overnight abstinent cigarette smokers aged 18–55	▪ Assess the acute effects of non-combustible PREPs for smokers.	▪ Ariva delivered less nicotine than OWN cigarettes and did not expose users to CO or increase heart rate; however, it failed to effectively suppress tobacco abstinence symptoms. ▪ Premarket evaluation of process designed to minimize toxicant exposure and maximize abstinence symptom suppression may be best method to realize public health potential of Ariva and other PREPs for tobacco users.

Funding Source: U.S. Public Health Service grants CA103827 and CA120142

Unintentional Child Poisonings Through Ingestion of Conventional and Novel Tobacco Products

Connolly GN, Richter P, Aleguas A Jr, Pechacek TF, Stanfill SB, Alpert HR. Pediatrics 2010; 125:896–9.

Type of Study	Type of Dissolvable(s)	Sample Size (N) / Subject Description	Objective(s)	Authors Conclusion(s)
National survey	▪ Camel Orbs pellets ("Fresh" and "Mellow")	▪ N=13,705 cases of tobacco ingestion among boys and girls <6 years of age from the National Poison Data System (2006–2008)	▪ Examine child poisonings nationwide resulting from ingestion of tobacco products. ▪ Assess potential toxicity of novel smokeless tobacco products to young children.	▪ >70% of cases in infants, snuff and chewing tobacco most common after cigarettes. ▪ Case of Orbs ingestion by 3-year-old in 2009. ▪ Orbs had 0.83 mg nicotine and 7.9 pH; 42% of nicotine in un-ionized form compared with <10% for cigarettes. ▪ Public health authorities advised to study dissolvable nicotine products to determine appropriate regulatory approach in light of their novelty and potential harm.

Funding Source: Not specified

Impact of Smokeless Tobacco Products on Cardiovascular Disease: Implications for Policy, Prevention, and Treatment: A Policy Statement from the American Health Association

Piano MR, Benowitz NL, FitzGerald GA, et al. Circulation 2010;122:1520–44.

Type of Study	Type of Dissolvable(s)	Sample Size (N) / Subject Description	Objective(s)	Authors Conclusion(s)
Review	▪ Ariva tobacco lozenges ▪ Stonewall tobacco lozenges ▪ Camel Orbs ▪ Came Sticks ▪ Camel Strips	Not applicable	▪ Review and summarize scientific evidence regarding SLT product use and potential cardiovascular risks associated with SLT product use that can be used to inform policy related to tobacco control and strategies related to tobacco harm reduction.	▪ Ariva and Stonewall contain 0.6–3.1 mg nicotine; Camel orbs 1 mg/orb; Camel sticks 3.1 mg/stick. ▪ Long-term SLT products use may be associated with increased risk of fatal myocardial infarction and stroke and some cancers and oral disease. ▪ No data on dissolvable tobacco products use and cardiovascular disease or other health risks.

Funding Source: Not specified

Brand Specific Responses to Smokeless Tobacco in a Rat Lip Canal Model

Schwartz JL, Brunnemann KD, Adami AJ, et al. J Oral Pathol Med 2010;39:453–9.

Type of Study	Type of Dissolvable(s)	Sample Size (N) / Subject Description	Objective(s)	Authors Conclusion(s)
Basic science study	▪ Stonewall	▪ N=75, Sprague Dawley rats 4–6 weeks of age, 5 groups with 15 rats per group	▪ Assess long-term mucosal changes induced by daily use of four different SLT formulas studied side-by-side and applied under identical protocols in animal model.	▪ All SLT products produced varying degrees of acute, subacute, and chronic inflammation in the stoma. ▪ Products (e.g., Stonewall) with lower levels of TSNAs and unprotonated nicotine caused less dysplasia. ▪ Findings consistent with model that tobacco with low levels of nitrosamines might potentially induce fewer carcinomas in human users.

Funding Source: NIDCR grant DE13222, Star Scientific grant, grant from University of Illinois at Chicago, Edward C. Wach Dental Research Fund

Findings

Publication Year 2011—5 articles

Oral Tobacco Products: Preference and Effects Among Smokers

Hatsukami DK, Jensen J, Anderson A, et al. Drug Alcohol Depend 2011;118:230–6.

Type of Study	Type of Dissolvable(s)	Sample Size (N) / Subject Description	Objective(s)	Authors Conclusion(s)
Randomized trial	▪ Ariva tobacco lozenges ▪ Stonewall tobacco lozenges	▪ N=99 (64 male) smokers interested in quitting entered the sampling phase and 91 completed the follow-up phase	▪ Assess smokers' preferences for five oral tobacco products that differed in formulation and dose of nicotine. ▪ Assess the effects of the selected products during a 2-week trial.	▪ With the exception of General Snus, a high nicotine product not preferred by any smoker, there were no differences across the other four tobacco products. ▪ Products with higher nicotine levels (Stonewall and Camel Snus) were rated more highly than products with lower nicotine (Ariva and Marlboro Snus). ▪ Camel Snus was associated with higher abstinence rates than Ariva and Stonewall.

Funding Source: R01-CA135884

US Smokers' Reactions To a Brief Trial of Oral Nicotine Products

O'Connor RJ, Norton KJ, Bansal-Travers M, Mahoney AC, Cummings KM, Borland R. Harm Reduct J 2011;8:1.

Type of Study	Type of Dissolvable(s)	Sample Size (N) / Subject Description	Objective(s)	Authors Conclusion(s)
Trial	▪Stonewall tablets	▪ N=67 ▪ Black, White, and other men and women smokers of at least ≥10 cigarettes/day for ≥1 year, not interested in quitting, and not currently using any other nicotine or tobacco product	▪ Examine smokers' interest in using a SLT or nicotine replacement product as a cigarette substitute.	▪ Commit lozenges most preferred; Stonewall least preferred (only 12% chose Stonewall for trial). ▪ 60% not at all likely to use Stonewall instead of cigarettes; 0% very likely to purchase in next year. ▪ Over 7-day trial, significant declines in cigarettes smoked/per day and exhaled CO, but no change in use of alternative products or salivary cotinine levels. ▪ Smokers more willing to use alternative product short term and nicotine replacement over a tobacco-based product.

Funding Source: NCI via Roswell Park Cancer Institute Transdisciplinary Tobacco Use Research Center (P50 CA114236)

Chemical Characterization of Dissolvable Tobacco Products Promoted To Reduce Harm

Rainey CL, Conder PA, Goodpaster JV. J Agric Food Chem 2011;59:2745–51.

Type of Study	Type of Dissolvable(s)	Sample Size (N) / Subject Description	Objective(s)	Authors Conclusion(s)
Basic science study	▪ Camel Orbs (Fresh and Mellow) ▪ Camel Mellow Sticks ▪ Camel Fresh Strips	▪ N=4 dissolvable Camel tobacco products (Mellow Orbs, Fresh Orbs, Mellow Sticks, Fresh Strips)	▪ Describe chemical characterization of four dissolvable tobacco products by gas chromatography-mass spectrometry.	▪ Nicotine, flavoring compounds (e.g., menthol, coumarin, cinnamaldehyde, vanillin, carvone, ethyl citrate), sweeteners (e.g., sorbitol, xylitol), binders (e.g., palmitic acid and stearic acid), and humectants (e.g., glycerin) were identified in the dissolvables. ▪ Chemical characterization, pH measurements, and nicotine quantification are the first to reveal the complexity of dissolvable tobacco products and may be used to assess potential oral health effects.

Funding Source: Not specified

Retail Promotions and Perceptions of R.J. Reynolds' Novel Dissolvable Tobacco in a US Test Market

Romito LM, Saxton MK, Coan LL, Christen AG. Harm Reduct J 2011;8:10.

Type of Study	Type of Dissolvable(s)	Sample Size (N) / Subject Description	Objective(s)	Authors Conclusion(s)
Audit and survey	▪ Camel Sticks ▪ Camel Strips ▪ Camel Orbs	▪ Random sample of retailers from 6 store categories (N=81) ▪ Awareness-Attitude Usage (AAU) survey of 243 Central Indiana adult male and female never, former, and current smokers	▪ Assess the availability, price, and point-of-purchase promotional strategies for Camel Dissolvables.	▪ Products carried by 46% of retail locations. ▪ Overall, 42% of consumers had heard of Camel Dissolvables, but percentages were higher for smokers. ▪ Interest and trial were low in all groups. ▪ Current retail promotional strategies appear to be targeting a select audience, primarily current smokers.

Funding Source: Internal grant from Indiana University Purdue University Indianapolis (IUPUI) Center for Research and Learning

RJ Reynolds Goes International With New Dissolvable Tobacco Products

Seidenberg AB, Rees VW, Connolly GN. Tob Control 2011; epublished October 7, 2011.

Type of Study	Type of Dissolvable(s)	Sample Size (N) / Subject Description	Objective(s)	Authors Conclusion(s)
Commentary	▪ Camel Orbs ▪ Came Sticks ▪ Camel Strips ▪ Revo "Orbs" ▪ Revo "Sticks" ▪ Revo "Strips" ▪ Ariva ▪ Stonewall ▪ Marlboro Sticks ▪ Skoal Sticks	▪ Camel orbs, sticks, and strips introduced into 3 US test markets in 2009 ▪ Nearly identical dissolvable tobacco products introduced into Taiwanese markets in 2010 under brand name Revo	▪ Not applicable	▪ Results of Camel Dissolvable and Revo product analyses not yet available to mainstream scientific community. ▪ Introduction of dissolvable tobacco products in other countries highlights need for improved global surveillance of these new products. ▪ Appropriate tobacco control policies and regulations must be applied.

Funding Source: NCI grant R01-CA125224

Questions?